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(54) Title: TREATMENT OF NICOTINE CRAVING AND/OR SMOKING WITHDRAWAL SYMPTOMS WITH AN ORAL COMPOSITION CONTAINING NICOTINE AND CAFFEINE OR XANTHINE

(57) Abstract

The subject invention encompasses an oral composition for the treatment or nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent.

Treatment of nicotine craving and/or smoking withdrawal symptoms with an oral composition containing nicotine and caffeine or xanthine

BACKGROUND OF THE INVENTION

The health hazards from smoking tobacco are well known. Of the many by-products of combustion found in cigarette smoke, the substances most studied have been tars, carbon monoxide, and nicotine. Tars are the agents linked to the causation of various cancers and pulmonary diseases such as emphysema and chronic bronchitis. Carbon monoxide is a deadly gas which reduces the ability of blood hemoglobin to carry sufficient oxygen. Carbon monoxide has also been causally linked to coronary artery disease and atherosclerosis. Nicotine appears to be the most pharmacologically active substance in tobacco smoke, yet it seems not to be as significant from a health standpoint as the tars and carbon monoxide. However, nicotine is the reinforcing substance in tobacco which maintains the addiction.

Various efforts have been made by smokers to discontinue smoking. Chewing beeswax, eating candy and peppermints as well as cold turkey interruption have been tried without much success. The addition of chemicals designed to sicken the user or render smoking repulsive to the user have also not produced good results. More recent therapies for smoking cessation have focused on the administration of nicotine to the smoker. These therapies allow the individual to satisfy a nicotine habit while minimizing or eliminating side effects caused by absorbing nicotine through the lungs along with the other harmful by-products of combustion of tobacco.

Nicotine supplementation has proven to be an effective therapy as an adjunct to smoking cessation in helping to reduce the craving for smoking and provide relief from smoking withdrawal symptoms. However, there are many smokers for whom nicotine supplementation alone is inadequate. In accordance with the present invention, it has been discovered that a composition can be formulated which provides the combination of nicotine and caffeine or caffeine equivalent in a single therapy. It has also been discovered that such a combination may offer the advantage of providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a broader spectrum of smokers who wish to break the smoking habit. It has further been discovered that these compositions may also curb the appetite which may aid in reducing the weight gain that is commonly experienced by individuals who stop smoking.

It is an object of the present invention to provide a composition comprising the combination of nicotine and caffeine or caffeine equivalent in a single therapy. It

is also an object of the present invention to deliver the nicotine and caffeine combination therapy in a convenient delivery system. It is a further object of the invention to provide methods for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms in individuals who wish to break or decrease the habit of smoking tobacco or the use of any tobacco product. These and other objects will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to an oral composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers from about 0.05mg to about 10mg of nicotine, and from about 0.1mg to about 250mg of caffeine or caffeine equivalent.

The present invention further relates to a method for providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment comprising the administration of a safe and effective amount of an oral composition comprising nicotine, and caffeine or caffeine equivalent.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention comprises nicotine, caffeine or caffeine equivalent, and preferably one or more pharmaceutically-acceptable carriers suitable for oral administration. These compositions are useful for the treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms.

The terms "nicotine craving" and "smoking withdrawal symptoms" as used herein both refer to any physical or psychological reaction relating to breaking the habit of smoking tobacco or using any tobacco product or decreasing the frequency or intensity of smoking tobacco or using any tobacco product.

In general, the descriptive term "pharmaceutically-acceptable" is used herein to describe materials that are non-toxic and suitable for administration to humans and/or lower animals. The term "pharmaceutically-acceptable carrier" as used herein means any material safe and effective for use in the compositions of the present invention. Such materials include pH adjusters, diluents, binders, lubricants, glidants, disintegrants, gum bases, elastomer solvents, liquid oral carriers, emollients, emulsifiers, buffering agents, solvents, preservatives, agents for regulating isotonicity, fillers, wetting agents, thickening agents, suspending agents, solubilizing agents, humectants, sweeteners, flavorings, plasticizers, bioadhesive compounds, surfactants, aromatic compounds, agents for aiding the film-forming properties and substantivity of the formulations, antimicrobials for maintaining the antimicrobial integrity of the

compositions, antioxidants, agents suitable for aesthetic purposes such as fragrances, pigments, and colorings, non-soluble ingredients, and mixtures thereof.

The terms "safe and effective amount", as used herein, mean a sufficient amount of material to provide the desired benefit without undue adverse side effects commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific safe and effective amount will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), and the specific formulation and optional components hereinafter.

The terms "suitable for oral administration", as used herein, refer to any formulation that is suitable for the convenient administration of the composition whereby the composition is taken into the mouth and swallowed, placed in contact with mucous membranes of the mouth, and/or throat and/or pharynx and dissolved slowly over a period of time, or taken into the mouth but not necessarily swallowed, e.g., chewing gum.

The following terms will be designated as follows: milligram as "mg", milliliter as "ml", nanogram as "ng", and microgram as "ug".

A detailed description of essential and optional components of the present invention is given below.

Nicotine

The present invention comprises nicotine. Nicotine is a tertiary amine composed of a pyridine and a pyrrolidine ring. It is a colorless to pale yellow, which is freely water soluble, strongly alkaline, hygroscopic liquid obtained from the tobacco plant. Nicotine has a characteristic odor and turns brown on exposure to air or light [Physicians Desk Reference, 48th Edition, p. 1306, 1984]. Nicotine is delivered in an amount of from about 0.05mg to about 10mg, preferably from about 0.25mg to about 7.5mg, and most preferably from about 0.5mg to about 3mg. Nicotine is also described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, p. 891, which is incorporated herein by reference.

Caffeine

The present inventions also comprise caffeine or a caffeine equivalent. Caffeine is found as white, fleecy masses or long, flexible, silky crystals. It is odorless, bitter tasting, and slightly soluble in water and alcohol. Caffeine may be derived synthetically or by extraction of coffee beans, tea leaves or kola nuts [Hawleys Condensed Chemical Dictionary, Twelfth Edition, 1993]. Examples of suitable sources of caffeine for use in the present invention are pure caffeine, caffeine combined with acetate, citrate, benzoate, phosphate, sulfate or salicylate. Also

suitable are any of the xanthine analogues that match caffeine's effectiveness as a central nervous system stimulant, including salts thereof that are compatible. Xanthine derivatives are described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1132-34, which is incorporated herein by reference. The caffeine or caffeine equivalent is delivered in an amount of from about 0.1mg to about 250mg, preferably from about 10mg to about 180mg, and most preferably from about 50mg to about 125mg.

Pharmaceutically-Acceptable Carrier

The invention compositions preferably also contain one or more pharmaceutically-acceptable carriers suitable for oral administration. Such compositions include (but are not limited to) lozenges, chewing gums, sublingual delivery systems, capsules, gelcaps, caplets, syrups, aqueous solutions, suspensions, or other formulations suitable for administering the present compositions orally. The present compositions also include formulations which deliver the nicotine and/or caffeine or caffeine equivalent in a sustained release system or at varying intervals or levels throughout the oral administration of the composition.

While the choice of oral carrier is not critical to the present invention, the carrier or carriers chosen must be suitable for administering the nicotine and caffeine or caffeine equivalent so that the desired blood levels of these compounds are achieved in the body of the recipient. The desired blood level of nicotine is from about 1ng/ml to about 100ng/ml, preferably from about 5ng/ml to about 75ng/ml, and most preferably from about 10ng/ml to about 50ng/ml, preferably within 1-4 hours of administration. The desired blood level of caffeine or caffeine equivalent is from about 0.01ug/ml to about 20ug/ml, preferably from about 0.1ug/ml to about 15ug/ml, and most preferably from about 0.5ug/ml to about 10ug/ml, preferably within 1-4 hours of administration.

The present compositions will normally be prepared in dosage unit form to contain safe and effective amounts of the nicotine and caffeine (or equivalent) to achieve the desired blood levels. Fractions of the dosage units or multiple dosage units may also be utilized. In general, the oral compositions herein deliver to a human or lower animal from about 0.05mg to about 10mg, preferably from about 0.25mg to about 7.5mg, and most preferably from about 0.5mg to about 3mg of nicotine; and from about 0.1mg to about 250mg, preferably from about 10mg to about 180mg, and most preferably from about 50mg to about 125mg, of caffeine or caffeine equivalent. Preferably, the present invention may be an oral composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent and one or more pharmaceutically-acceptable

carriers suitable for oral administration, wherein the composition delivers from about 0.05mg to about 10mg of nicotine, and from about 0.1mg to about 250mg of caffeine or caffeine equivalent.

The amount of nicotine and caffeine or caffeine equivalent and frequency of administration may vary depending on the carrier chosen and the personal needs of the user. However, it is suggested (as an example) that the present invention be administered from about once to about 12 times per day, preferably from about 3 to about 9 times per day, and most preferably from about 4 to about 8 times per day.

The compositions of the present invention may be in lozenge form. Lozenges are flavored solid dosage forms intended to be held in the mouth and sucked for slow dissolution and absorption by the oral mucosa. They may occur in various shapes and are generally formed either as compressed tablets or hard candies. Lozenges and their preparation are further described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1664-5, which is incorporated herein by reference.

Lozenges prepared by compression are prepared similarly to any compressed tablet. This process provides a hard tablet which is desirable for slow dissolution in the mouth. These lozenges may include: fillers such as dicalcium phosphate, spray dried lactose, microcrystalline cellulose; disintegrating agents, lubricants, and glidants.

Hard candy lozenges typically contain a base of sugar, flavored syrups such as high fructose corn syrups, and/or other carbohydrates. An example of such a base contains up to 92% corn syrup, up to 55% sugar, and from 0.1% to about 5% water. Additional ingredients may also be included such as flavorings, sweeteners, colorants, an adhesive substance such as mucilage or gum, acidulents, and the like. The base is heated and the lozenges are formed by molding and drying.

Lozenges may also be formulated with soft confectionery materials such as those contained in nougat. These materials generally contain a high boiling syrup such as corn syrup or the like, and a relatively light textured frappe. Typically the frappe is prepared from gelatin, egg albumen, milk proteins such as casein, and vegetable proteins such as soy protein, and the like. Flavorings oils, additional sugar, and sweeteners may also be added.

The present invention may also be in a solid oral dosage form. Solid oral dosage forms may be tablets, chewable tablets, caplets, capsules, gelcaps and other solid oral dosage forms known in the art. These forms include a buccal or sublingual tablet. Such a tablet is typically flat and oval and intended to be dissolved in the buccal pouch or beneath the tongue for absorption through the oral mucosa.

The tablets may be compressed, titurated, freeze dried, sugar or film coated, or multiply compressed. The tablets may also contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives and flow-inducing agents. In general, carrier materials suitable for preparation of unit dosage forms for oral administration are well-known in the art. Their selection will usually depend on taste, cost, and shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by one skilled in the art. Techniques and compositions for oral solid dosage forms suitable for the present invention are described in Remington's Pharmaceutical Sciences, 18th Edition, 1990, pp. 1633-75, which is incorporated herein by reference.

The present compositions may also be in the form of a chewing gum. Such formulations typically comprise a gum base, elastomer solvents, plasticizers or softeners, fillers, flavorings, colorants, emulsifiers, and sweeteners. The gum base may be any water-insoluble gum base which includes (but is not limited to): natural elastomers including substances of vegetable origin such as chicle, jelutong, gutta percha, and crown gum; rubbers; and synthetic elastomers such as butadiene-styrene polymers, polyethylene, polyisobutylene, polyvinylacetate, and mixtures thereof. The gum base may be present at a level of from about 5% to about 45%, and preferably from about 15% to about 25%, by weight of the composition.

Examples of suitable elastomer solvents may comprise methyl, glycerol or pentaerythritol esters of rosins or modified rosins, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. The elastomer solvents may be present at a level of from about 5% to about 75%, and preferably from about 35% to about 70%, by weight of the composition.

Plasticizers or softeners may also be included to achieve a variety of textures and consistency properties. Such ingredients include without limitation: lanolin, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glycerin, natural waxes, petroleum waxes, microcrystalline waxes, and mixtures thereof. Plasticizers or softeners may be present at a level of up to about 30%, and preferably from about 3% to about 20%, by weight of the composition. Fillers such as aluminum hydroxide, alumina, aluminum silicates, calcium carbonate, talc and mixtures thereof, may also be included at a level of from about 4% to about 30%, by weight of the composition.

The present compositions may contain one or more solvents. Suitable solvents include but are not limited to water, alcohol, propylene glycol, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients.

The present invention may also be in a liquid oral dosage form. Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, pseudo emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules. These dosage forms also contain suitable solvents, emulsifying agents, buffering agents, suspending agents, diluents, natural and artificial sweeteners, coloring agents, and flavoring agents. Antioxidants such as butylated hydroxy anisole or butylated hydroxy toluene, and preservatives such as methyl or propyl paraben or sodium benzoate may also be included. Specific examples of carriers and excipients that may be used to formulate oral dosage forms, are described by Roberts in U.S. Patent 3,903,297, issued September 2, 1975, which is incorporated herein by reference.

Water-insoluble or poorly soluble ingredients, generally in base form, may also be incorporated into aqueous-based orally acceptable carriers such as dispersions, suspensions, oil-in-water emulsions and the like by means of suitable dispersing, suspending or emulsifying agents, respectively, which are readily apparent to those skilled in the art of formulations.

In preparing the liquid oral dosage forms, the active components are incorporated into an aqueous-based orally acceptable carrier consistent with conventional practices. An "aqueous-based orally acceptable carrier" is one wherein the entire or predominant solvent content is water. Typical carriers include simple aqueous solutions, syrups, dispersions and suspensions, and aqueous based emulsions such as the oil-in-water type. The most preferred carrier is a suspension or solution of the phosphate derivative and active in an aqueous vehicle containing a suitable suspending or solubilizing agent. Suitable suspending agents include celluloses, carboxymethyl cellulose and its salts, guar gum and the like. Suitable solubilizing agents include sucrose solutions, ethanol, and surfactants such as polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides (e.g., Polysorbate 80). Suspension systems, suspension and solubilizing agents, and methods for their use are described in M. Pernarowski, "Solutions, Emulsions and Suspensions" Remington's Pharmaceutical Sciences (A. Osol, editor, 15th Edition, 1975), which is incorporated herein by reference.

Although water itself may make up the entire liquid carrier, typical oral formulations also contain a co-solvent including but not limited to alcohol, propylene glycol, glycerin, sorbitol solution, and the like, to assist solubilization and incorporation of water-insoluble ingredients, flavoring oils and the like into the composition. In general, the compositions may contain from about 5 to about 25

volume/volume percent of the co-solvent, most preferably from about 10 to about 20 volume/volume percent of the co-solvent.

Non-aqueous carriers may also be used in the present compositions. Non-aqueous carriers include, without limitation, oil of animal, mineral or vegetable origin such as almond oil, olive oil, safflower oil, sunflower oil, and sucrose polyester (sold under the brand name Olestra)..

The compositions may also comprise from about 0% to about 10%, preferably from about 2% to about 5%, of one or more pharmaceutically-acceptable emulsifiers. These emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dicert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986); the disclosures of which are incorporated herein by reference. Preferred emulsifiers are anionic or nonionic, although the other types may also be used.

Diluents, binders, lubricants, glidants, and disintegrants may also be included at al level of from about 0% to about 25%, and preferably from about 2% to about 20%, by weight of the composition. Suitable diluents include microcrystalline cellulose, mannitol, dicalcium phosphate, and celluloses. Binders useful include starch; gelatin; sugars such as sucrose, glucose and dextrose; natural and synthetic gums such as acacia, sodium alginate, ghatti gum, carboxymethylcellulose, and polyvinylpyrrolidine; polyethylene glycol, water, and alcohol. Lubricants include talc, magnesium stearate, stearic acid, polyethylene glycol, and hydrogenated vegetable oils. Glidants include colloidal silicon dioxide and disintegrants include starches, clays, celluloses, algins, gums, and cross-linked polymers.

The present invention may also comprise one or more bioadhesive compounds which adhere to moist area of biological membranes. Such compounds include sodium carboxymethylcellulose, amyopectin, hydroxyethylcellulose, acrylates, gelatins, guar gum, karaya gum, tragacanth, agar, alginc acid, calcium carboxymethylcellulose, dextrin, methylcellulose, pectin, polyethylene glycol and polyvinylpyrrolidone. The bioadhesive compounds may be present at a level of from about 0.1% to about 30%, and preferably from about 7% to about 25%, by weight of the composition.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, sodium benzoate, ascorbic acid, thimerosal, chlorobutanol, phenylmercuric acetate or benzalkonium chloride may also be employed. Preferred are parabens, preservative system for use herein comprises a

combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from about 0.001% to about 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The compositions of the present invention also include microencapsulation of either the nicotine or caffeine (or caffeine equivalent) or both. Techniques and materials for microencapsulation are well known in the art. Microencapsulation is discussed more fully in Kirk and Othmer's Encyclopedia of Chemical Technology, Vol. 13, 2nd Edition, pp.436-456, which is incorporated herein by reference. The nicotine and/or caffeine may also be protectively coated using techniques known in the art, such as an enteric coating, to protect the compounds in the gastrointestinal tract.

The compositions of the present invention may also contain one or more aromatic components. These aromatics include, for example, menthol, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); 2-dodecenal (citrus, mandarin); thymol; cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine; 3-l-menthoxy propane-1,2-diol; N-substituted-p-menthane-3-carbox-amides and acyclic carboxamides; and mixtures thereof. Preferred are menthol, eucalyptol, thymol, cedar leaf oil, myristica oil, lavender oil, nutmeg oil, turpentine, and mixtures thereof. Aromatic compounds may be present at a level of from about 0.0001% to about 1%, preferably from about 0.001% to about 1%, and most preferably from about 0.001% to about 0.5%, by weight of the compositions.

The present compositions may also contain one or more flavorings. Suitable flavorings include both natural and artificial flavors, spearmint, peppermint, wintergreen, cinnamon, anise, vanilla, fruit essences including apple, peach, pear, strawberry, raspberry, cherry, pineapple, and the like, or any other flavorings that will effectively mask the taste of the nicotine and caffeine or caffeine equivalent. Preferred are peppermint, spearmint, anise, and fruit essences. Flavorings may be present at levels of from about 0% to about 5%, and preferably from about 0.5% to about 3%, by weight of the compositions.

Sweetening agents suitable for use herein include any sweetener commercially available and suitable for human consumption such as sugars such as sucrose, glucose, dextrose, fructose, saccharin and its various salts, cyclamic acid and its salts, dipeptide sweeteners such as aspartame, and mixtures thereof.

A variety of additional optional pharmaceutically-acceptable ingredients may also be added to the present invention compositions. These additional ingredients include pH adjusters such as sodium hydroxide; buffering agents such as sodium bicarbonate; humectants such as urea, glycerol, sorbitols and glycerin; thickeners such as methylcellulose, xanthan gum, and carbomer; surfactants such as Tween 80 and Polyoxyl 40 Stearate; various polymers for aiding the film-forming properties and substantivity of the formulations; antimicrobials for maintaining the antimicrobial integrity of the compositions; antioxidants; and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions may also contain low levels of pharmaceutically-acceptable insoluble ingredients added, for example, for visual effect purposes, e.g., thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available form Hallcrest, Glenview, Illinois 60025, U.S.A.

Method of Treatment

The method of providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment as disclosed herein comprises the administration of a safe and effective amount of an oral composition comprising nicotine, and caffeine or caffeine equivalent. Such compositions preferably further comprise one or more pharmaceutically-acceptable carriers suitable for oral administration.

While it is preferred that the nicotine and caffeine or caffeine equivalent are administered in an oral carrier composition comprising both nicotine and caffeine (or caffeine equivalent), it is also within the scope of the present invention that the desired blood levels of nicotine and caffeine be achieved through concurrent administration of nicotine and caffeine (or caffeine equivalent) but not necessarily by a carrier which comprises both compounds. For example, it is within the scope of the present invention that caffeine be administered in a tablet formulation and that nicotine be administered concurrently by a transdermal delivery system. Another example is the administration of nicotine by an aqueous nasal spray and concurrent administration of caffeine by chewing gum.

Therefore the present invention also encompasses a method for providing treatment and/or relief of nicotine craving and/or smoking withdrawal symptoms to a human or lower animal in need of such treatment, comprising administering a safe and effective amount of nicotine and concurrently administering a safe and effective amount of caffeine or caffeine equivalent. The terms "concurrently" and

"concurrent", as used herein, mean that the safe and effective amounts of nicotine and caffeine or caffeine equivalent are administered simultaneously or within 6 hours of each other.

Therefore it is in accordance with the present invention, that nicotine and/or caffeine or caffeine equivalent may be concurrently administered through a variety of embodiments or carriers as long as the desired blood levels taught in the present invention are achieved. Such embodiments or carriers include without limitation: intranasal delivery systems such as nasal drops, nasal sprays, nasal gels, ointments applied in the nasal cavity and systems which allow for the inhalation of vapors produced by nicotine or caffeine (or caffeine equivalent); transdermal and transmucosal delivery systems; and oral delivery systems or carriers such as those disclosed herein.

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE I

The following is a lozenge composition of the present invention.

Ingredient	Weight %
Sorbitol	17.00
Mannitol	16.50
Starch	13.60
Sweetener	1.20
Flavor	11.70
Color	0.10
Polyacrylic acid (34%)[1]	12.80
Corn syrup	24.60
Nicotine	.01
Caffeine	2.50

[1]Polyacrylic acid polymer having a mass average molecular weight of about 4500 available from Rohm and Haas

The above ingredients are prepared according to methods known in the art.

EXAMPLE II

The following is a chewing gum composition of the present invention.

Ingredient	Weight %
Sorbitol crystals	36.44
Jelutong gum base	18.5
Sorbitol (70% Aqueous solution)	18.5
Mannitol	10.00
Glycerin	7.56
Flavor	1.00
Polyacrylic acid (as in Example I)	3.00
Nicotine	0.02
Caffeine	5.00

The above ingredients are prepared according to methods known in the art.

EXAMPLE III

Liquid Oral Dosage Form

A liquid oral dosage form composition according to the present invention is prepared having the following components:

Ingredient	Weight %
Sucrose (xfine granular)	49.00
Polysorbate 80	0.02
Glycerin	2.00
Propylene Glycol	15.00
Sodium Citrate, dihydrate	0.522
Citric Acid	0.338
Potassium Sorbate	0.10
Caffeine	2.00
Nicotine	0.01
Flavor	0.30
Distilled Water	20.71
Alcohol	10.00

Mix together sucrose and about 1/3 the amount of water and heat to about 60°C until sucrose is dissolved. Mix in Polysorbate 80 and glycerin. Separately mix together propylene glycol, sodium citrate dihydrate, citric acid and about 1/3 the amount of water. Separately mix together potassium sorbate and about 1/3 the amount of water. Add flavor. Mix together sucrose solution with propylene glycol solution. Mix together this solution and potassium sorbate solution. Lastly, add flavor solution. Adjust water level for proper batch size. Adjust pH to about 6.5-8.5. Mix for 30-35 minutes.

What is Claimed is:

1. An oral composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine and caffeine or caffeine equivalent, wherein the composition delivers:
   a) from 0.05mg to 10mg of nicotine; and
   b) from 0.1mg to 250mg of caffeine or caffeine equivalent.

2. The composition according to Claim 1 wherein (b) is caffeine.

3. An oral composition for the treatment of nicotine craving or smoking withdrawal symptoms comprising nicotine, caffeine or caffeine equivalent, and one or more pharmaceutically-acceptable carriers suitable for oral administration, wherein the composition delivers:
   a) from 0.05mg to 10mg of nicotine; and
   b) from 0.1mg to 250mg of caffeine or caffeine equivalent.

4. The composition according to Claim 3 wherein the composition is in the form of a hard candy lozenge comprising from 75% to 92% of corn syrup, and from 30% to 55% sugar.

5. The composition according to Claim 4 wherein (b) is caffeine.

6. The composition according to Claim 4 wherein (b) is the caffeine equivalent xanthine.

7. The oral composition according to Claim 3 comprising:
   a) from 0.25mg to 7.5mg of nicotine; and
   b) from 10mg to 180mg of caffeine or caffeine equivalent.

8. The composition according to Claim 7 wherein the composition is in the form of a chewing gum comprising from 5% to 45% of a gum base, from 5% to 75% of at least one elastomer solvents, and from 0% to 5% of one or more flavorings.

9. The composition according to Claim 8 wherein the flavorings are selected from the group consisting of peppermint, spearmint, anise, and fruit essences.

10. The composition according to Claim 9 further comprising from 1% to 30% of a plasticizer or softener.

11. The composition according to Claim 10 further comprising from 0.1% to 5% of one or more sweeteners.

12. The composition according to Claim 7 wherein the composition is in the form of a lozenge.

13. The composition according to Claim 7 wherein the composition is in the form of a sublingual tablet.

14. The composition according to Claim 7 wherein the nicotine and/or caffeine or caffeine equivalent is protectively coated by microencapsulation or enteric coating.

INTERNATIONAL SEARCH REPORT

Intern: ıl Application No
PCT/US 95/07381

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/52 A61K9/00 //(A61K31/52,31:465)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,91 01132 (FERTIN LAB. LTD.) 7 February 1991 see page 18 - page 19 see claims 14,15 ---	1-14
Y	DE,A,19 01 277 (PARTIPHARM AG) 6 August 1970 see the whole document ---	1-14
Y	EP,A,0 472 428 (WM. WRIGLEY JR. COMP.) 26 February 1992 see the whole document ---	1-14
Y	US,A,4 778 677 (G.K. EBBESEN) 18 October 1988 see the whole document --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1995	13. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stierman, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TOXICOL APPL PHARMACOL (UNITED STATES), JUN 30 1985, VOL. 79, NO. 2, PAGE(S) 268-73, Tariq M et al 'Effect of nicotine and caffeine pretreatment on the gastric mucosal damage induced by aspirin, phenylbutazone, and reserpine in rats.' see the whole document ---	1-14
Y	J. OF NEUROCHEMISTRY, vol.61, no.5, 1993 pages 1901 - 1906 Wilson S P 'Pertussis toxin enhances proenkephalin synthesis in bovine chromaffin cells' see the whole document ---	1-14
Y	DE,A,35 06 406 (STROMBERG H.-J.) 28 August 1986 see the whole document ---	1-14
Y	PHARMACOL BIOCHEM BEHAV (UNITED STATES), APR 1994, VOL. 47, NO. 4, PAGE(S) 919-36, Cohen C et al 'Caffeine antagonizes EEG effects of tobacco withdrawal.' see the whole document ---	1-14
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Y	US,A,5 288 497 (T.H. STANLEY ET AL.) 22 February 1994 see the whole document see claims 163,199,219 ---	1-14
Y	US,A,4 568 676 (J.B. SMITH) 4 February 1986 see the whole document ---	1-14
Y	PHARMAZIE, 1977, VOL. 32, PAGE(S) 511-15 El-Banna, H. M. et al 'The application of solid dispersion technique in the preparation of therapeutic tablets. Part 1: Paracetamol, amylobarbitone, and caffeine tablets' see the whole document ---	1-14
Y	DE,A,16 17 418 (CHEM. WERKE ALBERT) 25 March 1971 see the whole document --- -/--	1-14

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 95/07381

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ADDICT BEHAV (ENGLAND), MAY-JUN 1994, VOL. 19, NO. 3, PAGE(S) 229-56, Swanson JA et al 'Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal.' see the whole document	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/07381

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4, 7-14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The expressions "an oral composition", "caffeine equivalent" does not make sufficiently clear, which compositions/compounds are meant. The search has therefore been restricted to the compositions and compounds explicitly mentioned in the claims and to the general inventive concept.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 95/07381

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